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Doherty, Dennis E; Bleecker, Eugene R; Moroni-Zentgraf, Petra; Zaremba-Pechmann, Liliana; Kerstjens, Huib A M

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Original Article

Tiotropium Respimat Efficacy and Safety in Asthma: Relationship to Age

Dennis E. Doherty, MD[a], Eugene R. Bleecker, MD[b], Petra Moroni-Zentgraf, MD[c], Liliana Zaremba-Pechmann, PhD[d], and Huib A.M. Kerstjens, MD[e] *Lexington, Ky; Tucson, Ariz; Sydney, Australia; Biberach an der Riss, Germany; and Groningen, The Netherlands*

What is already known about this topic? There is a perception that there is a differential response to bronchodilators in older compared with younger patients with asthma, yet this perception is based on limited data.

What does this article add to our knowledge? The current analyses demonstrate that the bronchodilator efficacy and safety of tiotropium Respimat is not impacted by age in patients with symptomatic moderate or severe asthma.

How does this impact current management guidelines? These results have important therapeutic implications, because there is an increase in the aging population worldwide as well as increased prevalence of asthma in older individuals.

BACKGROUND: Data are limited on the differential response to long-acting bronchodilators in older versus younger adults with asthma.
OBJECTIVE: To determine whether the response to tiotropium Respimat differed in older versus younger patients with asthma.
METHODS: *Post hoc* analyses of 4 randomized, double-blind, placebo-controlled studies in adults with asthma were carried out. Two studies compared tiotropium Respimat 5 μg once daily with placebo, both added to high-dose inhaled corticosteroid (ICS) plus long-acting β_2-agonist (ie, severe asthma). The other 2 evaluated tiotropium Respimat 2.5 or 5 μg once daily, salmeterol 50 μg twice daily, or placebo, all added to medium-dose ICS (moderate asthma). Data were analyzed in 2 pools: (1) severe and (2) moderate asthma. Efficacy end points: trough and peak FEV_1; trough forced vital capacity; Asthma Control Questionnaire total score and responder percentage, all at week 24. One set of analyses was performed with age as a continuous covariate; the second was conducted in categories less than 40, 40 to 60, and more than 60 years, with treatment-by-age subgroup interaction *P* values obtained. Safety was analyzed in age categories.
RESULTS: Across the age categories, treatment-by-age subgroup interaction *P* values for trough FEV_1 were .13 and .77 for patients with severe and moderate asthma, respectively, not indicating significant impact of age on overall treatment effect, with this observation replicated in the 2 continuum analyses. The other end points (including safety) were also not impacted by age.
CONCLUSIONS: Once-daily tiotropium Respimat add-on to ICS or ICS/long-acting β_2-agonist therapy was effective and well tolerated in patients with asthma independent of age. **(J Allergy Clin Immunol Pract 2020;8:2653-60)**

Key words: *Aging; Asthma; Long-acting β_2-agonists; Long-acting muscarinic antagonist; Pharmacotherapy*

[a]University of Kentucky, Lexington, Ky
[b]University of Arizona, Tucson, Ariz
[c]Boehringer Ingelheim Pty. Ltd., Sydney, NSW, Australia
[d]Boehringer Ingelheim, Biberach an der Riss, Germany
[e]University of Groningen, University Medical Center Groningen, and Groningen Research Institute for Asthma and COPD, Groningen, The Netherlands

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Corresponding author: Dennis E. Doherty, MD, 4852 Waterside Dr, Lexington, KY 40513. E-mail: dedohe0@email.uky.edu.
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List of abbreviations
ACQ- Asthma Control Questionnaire
ICS- Inhaled corticosteroid
LABA- Long-acting β_2-agonist

INTRODUCTION

Inhaled corticosteroids (ICSs) are the primary controller therapy recommended for the management of persistent asthma in adults.[1] For patients with more than just occasional symptoms, the current Global Initiative for Asthma report recommends daily low-dose ICS alone, or as-needed use of low-dose ICS plus the long-acting β_2-agonist (LABA) formoterol.[1] If this is insufficient to control a patient's asthma, the Global Initiative for Asthma recommends regular use of an ICS-LABA combination, with the ICS dose gradually increased, and the long-acting muscarinic antagonist tiotropium an add-on option for patients with asthma that is uncontrolled with medium- or high-dose ICS plus LABA. Indeed, tiotropium Respimat has been shown to be an effective add-on therapy to ICS plus LABA or to ICS alone in patients with symptomatic asthma,[2-4] and is now approved for use as asthma maintenance treatment for patients from age 6 years in many countries, including the United States and throughout the European Union (see local label for further details).

There is a perception that there is a differential response to bronchodilators in older compared with younger patients with asthma. This perception is perhaps based on an early study evaluating the short-acting β_2-agonist albuterol and the short-acting muscarinic antagonist ipratropium[5]; to our knowledge, no studies have evaluated the effect of age on the effectiveness of long-acting bronchodilators. Because asthma impacts individuals of all ages, with, for example, the US prevalence of asthma in those 65 years or older (7.8%) being similar to that in children (7.5%),[6] the current *post hoc* analyses were therefore conducted to evaluate the response to tiotropium Respimat across the 18 to 75 years age range of adults with symptomatic moderate or severe asthma, when added-on to ICS or ICS/LABA maintenance therapy.

METHODS

These are analyses of data from 4 phase III, randomized, double-blind, placebo-controlled studies. The first 2 studies were PrimoTinA-asthma (NCT00776984 and NCT00772538), which compared tiotropium Respimat 5 μg once daily with placebo, both added to high-dose ICS (≥800 μg budesonide or equivalent) plus LABA over 48 weeks.[2] The other 2 studies were MezzoTinA-asthma (NCT01172808 and NCT01172821), which evaluated tiotropium Respimat 2.5 μg or 5 μg once daily, salmeterol 50 μg twice daily via hydrofluoroalkane pressurized metered-dose inhaler, or placebo, individually added to medium-dose ICS (400-800 μg budesonide or equivalent) over 24 weeks.[3] Data were analyzed in 2 pools—one including the 2 PrimoTinA-asthma (severe asthma) studies, and the other including the 2 MezzoTinA-asthma (moderate asthma) studies.

Participants

Full inclusion and exclusion criteria for the 4 studies have been published previously.[2,3] In brief, all patients were aged 18 to 75 years, symptomatic (Asthma Control Questionnaire [ACQ] mean score ≥1.5), with the diagnosis of asthma having been made before the age of 40 years, and either lifelong nonsmokers or ex-smokers (<10 pack-years, with no smoking in the year before enrollment). Patients with a diagnosis of chronic obstructive pulmonary disease were excluded. All patients provided written informed consent before any study-related procedure. The studies were approved by the independent ethics committees or research boards at each institution, and were performed in accordance with the principles of the Declaration of Helsinki, and the International Conference on Harmonization notes for guidance on Good Clinical Practice (ICH/CPMP/135/95).

Outcomes

Coprimary end points of all 4 studies were trough FEV_1 response (assessed within 10 minutes before study medication), and peak FEV_1 within 3 hours postdose, both at week 24. Secondary end points included trough forced vital capacity, mean ACQ total score, and the percentage of ACQ responders (defined as an improvement in ACQ score of at least 0.5 points from baseline; this was a coprimary end point in the 2 MezzoTinA-asthma studies) at week 24. The data reported in this article are from *post hoc* analyses of these end points, with one set of analyses performed with age as a continuous covariate ("continuum analyses") and the second set of analyses conducted in patients subgrouped in the categories age less than 40, 40 to 60, and more than 60 years ("subgroup analyses"). Safety data by age category were also analyzed. Some of the tiotropium versus placebo data from the subgroup analyses have previously been published,[7,8] but none of the salmeterol data or the continuum analyses have been published.

Sample size and statistical methods

The analyses presented in this article were not formally powered, and are *post hoc* and exploratory in nature.

Three different sets of models were run—1 set for the continuum analyses and 2 for the subgroup analyses. In all 3 sets, trough and peak FEV_1, trough forced vital capacity, and ACQ total score were analyzed using mixed-effects models that included "treatment," "study," "visit," and "treatment-by-visit" as fixed, categorical effects and "baseline" and "baseline-by-visit" as fixed, continuous covariates (where "baseline" is the value of the respective variable assessed predose on day 1); ACQ responder rate was analyzed using logistic regression models that included "treatment" and "study." The first set of models, run for the continuum analyses, was used across the full age range and included age as a continuous covariate. The second set of models was used to obtain the results within the age subgroups. The third set of models was used across the age subgroups to derive the interaction *P* value, and included "age subgroup" and "age_subgroup-by-treatment" interaction.

RESULTS

Participants

The current analyses included data from 912 patients in PrimoTinA-asthma and 2100 patients in MezzoTinA-asthma. Their baseline demographic and disease characteristics are presented in Table I. The mean age of patients in PrimoTinA-asthma was 53.0 years, and in MezzoTinA-asthma 43.1 years.[2,3] Other than age, the only consistent differences between the 3 age groups were asthma duration on entry to the studies and bronchodilator reversibility in liters, but not in percent.

Outcomes

In the continuum analyses, bronchodilator efficacy versus placebo in terms of trough FEV_1 was consistently in favor of

TABLE I. Baseline demographic and disease characteristics

	PrimoTinA-asthma		MezzoTinA-asthma			
Characteristic	**Tiotropium Respimat 5 μg QD (n = 456)**	**Placebo (n = 456)**	**Tiotropium Respimat 2.5 μg QD (n = 519)**	**Tiotropium Respimat 5 μg QD (n = 517)**	**Salmeterol 50 μg BID (n = 541)**	**Placebo (n = 523)**
No. of patients						
<40 y	69	67	209	193	237	217
40-60 y	258	239	259	261	253	258
>60 y	129	150	51	63	51	48
Sex: female, %						
<40 y	59	52	56	52	50	53
40-60 y	59	65	66	62	64	62
>60 y	63	59	59	60	63	73
Age (y)						
<40 y	31 ± 6	32 ± 6	31 ± 6	31 ± 6	30 ± 6	30 ± 6
40-60 y	51 ± 6	52 ± 6	49 ± 6	49 ± 6	49 ± 6	49 ± 6
>60 y	66 ± 4	66 ± 4	65 ± 4	65 ± 4	65 ± 3	66 ± 4
Body mass index (kg/m^2)						
<40 y	27 ± 7	27 ± 6	25 ± 6	26 ± 7	25 ± 6	26 ± 7
40-60 y	29 ± 6	29 ± 7	28 ± 6	28 ± 6	28 ± 6	28 ± 6
>60 y	28 ± 5	28 ± 5	29 ± 8	28 ± 5	29 ± 7	28 ± 5
Smoking status, %						
Never smoked						
<40 y	78	69	87	86	87	94
40-60 y	73	76	82	79	81	81
>60 y	75	83	82	78	69	83
Ex-smoker						
<40 y	22	31	13	14	13	6
40-60 y	27	24	18	21	19	19
>60 y	25	17	18	22	31	17
Smoking history (pack-years)						
<40 y	4.2 ± 3.1	4.0 ± 2.6	2.5 ± 2.1	4.0 ± 2.5	3.3 ± 2.8	3.4 ± 2.0
40-60 y	5.0 ± 2.6	5.1 ± 2.5	4.8 ± 2.8	4.6 ± 3.3	4.5 ± 2.7	4.0 ± 2.5
>60 y	6.6 ± 2.7	4.5 ± 3.0	4.6 ± 3.6	4.9 ± 2.8	4.6 ± 2.6	6.1 ± 2.6
Duration of asthma (y)						
<40 y	20 ± 9	22 ± 8	15 ± 11	14 ± 11	13 ± 10	14 ± 11
40-60 y	27 ± 13	28 ± 13	24 ± 14	26 ± 13	24 ± 13	24 ± 13
>60 y	39 ± 12	41 ± 13	38 ± 12	40 ± 14	39 ± 14	38 ± 12
FEV_1 % predicted prebronchodilation*						
<40 y	55 ± 12	52 ± 13	74 ± 8	72 ± 8	74 ± 8	74 ± 8
40-60 y	55 ± 12	56 ± 12	72 ± 8	72 ± 8	72 ± 8	73 ± 8
>60 y	54 ± 13	55 ± 12	71 ± 7	71 ± 8	73 ± 8	73 ± 8
FEV_1 % predicted postbronchodilation*						
<40 y	63 ± 12	59 ± 13	91 ± 10	88 ± 10	90 ± 11	90 ± 10
40-60 y	62 ± 13	63 ± 13	88 ± 11	87 ± 11	89 ± 12	89 ± 11
>60 y	60 ± 13	62 ± 13	89 ± 14	87 ± 16	88 ± 10	88 ± 11
FVC % predicted prebronchodilation*						
<40 y	78 ± 16	77 ± 17	93 ± 12	92 ± 13	92 ± 12	93 ± 13
40-60 y	80 ± 16	79 ± 16	95 ± 14	95 ± 14	95 ± 14	97 ± 14
>60 y	80 ± 17	80 ± 17	97 ± 14	97 ± 13	97 ± 14	98 ± 16
FVC % predicted postbronchodilation*						
<40 y	86 ± 15	85 ± 15	103 ± 12	102 ± 13	101 ± 12	103 ± 11
40-60 y	88 ± 16	87 ± 16	106 ± 14	106 ± 14	107 ± 15	108 ± 14
>60 y	87 ± 18	91 ± 17	112 ± 19	111 ± 15	110 ± 16	108 ± 17
FEV_1/FVC % postbronchodilator						
<40 y	63 ± 7	59 ± 8	76 ± 9	74 ± 9	76 ± 10	75 ± 8
40-60 y	60 ± 8	61 ± 8	70 ± 9	70 ± 9	70 ± 9	69 ± 9
>60 y	57 ± 9	56 ± 10	65 ± 11	64 ± 8	66 ± 8	68 ± 9

(continued)

TABLE I. *(Continued)*

Characteristic	PrimoTinA-asthma		MezzoTinA-asthma			
	Tiotropium Respimat 5 μg QD (n = 456)	Placebo (n = 456)	Tiotropium Respimat 2.5 μg QD (n = 519)	Tiotropium Respimat 5 μg QD (n = 517)	Salmeterol 50 μg BID (n = 541)	Placebo (n = 523)
FEV_1 reversibility (L)						
<40 y	0.319 ± 0.257	0.281 ± 0.283	0.579 ± 0.283	0.516 ± 0.236	0.544 ± 0.250	0.552 ± 0.248
40-60 y	0.219 ± 0.201	0.223 ± 0.240	0.456 ± 0.208	0.431 ± 0.204	0.471 ± 0.264	0.445 ± 0.194
>60 y	0.149 ± 0.167	0.186 ± 0.159	0.410 ± 0.231	0.378 ± 0.244	0.374 ± 0.134	0.342 ± 0.143
FEV_1 reversibility (%†)						
<40 y	19 ± 19	17 ± 18	24 ± 12	22 ± 9	22 ± 10	22 ± 10
40-60 y	15 ± 14	16 ± 17	23 ± 9	21 ± 10	23 ± 12	22 ± 9
>60 y	13 ± 14	15 ± 14	25 ± 14	23 ± 15	21 ± 7	22 ± 9
ICS dose of stable maintenance treatment (μg)‡						
<40 y	1224 ± 521	1230 ± 544	642 ± 208	634 ± 218	639 ± 223	654 ± 229
40-60 y	1159 ± 545	1181 ± 540	663 ± 220	681 ± 214	660 ± 191	682 ± 213
>60 y	1239 ± 485	1231 ± 580	679 ± 202	682 ± 213	659 ± 186	661 ± 182

BID, Twice daily; *FVC*, forced vital capacity; *QD*, once daily.
Treated set (pooled data). All values are mean ± SD except where indicated.
*Measured at visit 1(screening).
†Percentage change from pre- to postbronchodilator value.
‡Budesonide or equivalent dose.

tiotropium and not influenced by age (Figure 1, *A*, shows the results for patients with severe asthma, with the results for patients with moderate asthma shown in Figure 1, *B*). This was also demonstrated in the subgroup analyses, in which the treatment-by-age subgroup interaction *P* values were both nonsignificant ($P = .13$ for patients with severe asthma [Figure 1, *C*], and $P = .77$ for patients with moderate asthma [Figure 1, *D*]).

The analyses of peak FEV_1 were similar to trough FEV_1, with no clear influence of age on bronchodilator efficacy in either the patients with severe asthma (Figure 2, *A*; see Figure E1, *A*, in this article's Online Repository at www.jaci-inpractice.org) or the patients with moderate asthma (Figure 2, *B*, and Figure E1, *B*), and nonsignificant treatment-by-age subgroup interactions ($P = .57$ and .97 for patients with severe and moderate asthma, respectively). Furthermore, age did not impact trough forced vital capacity in patients with severe (Figure 3, *A*; see Figure E2, *A*, in this article's Online Repository at www.jaci-inpractice.org) or moderate asthma (Figure 3, *B*, and Figure E2, *B*); the interaction *P* values were .052 and .47, respectively.

In patients with severe asthma, the effect of the addition of tiotropium Respimat 5 μg once daily on mean ACQ total score was not influenced by age, neither in the continuum analysis (Figure 4, *A*) nor in the subgroup analysis (see Table E1 in this article's Online Repository at www.jaci-inpractice.org), with a nonsignificant treatment-by-age subgroup interaction ($P = .13$). Similarly, in patients with moderate asthma, age did not influence the effect of tiotropium Respimat on mean ACQ total score (Figure 4, *B*; see Table E2 in this article's Online Repository at www.jaci-inpractice.org); the overall treatment-by-age subgroup interaction was nonsignificant ($P = .49$). In both the subgroup analysis and the continuum analysis, there was a slight decrease in salmeterol efficacy with increasing age in patients with moderate asthma.

In the ACQ responder analyses with continuous age, there was a slight influence of age in both moderate and severe asthma, with a trend toward decreasing efficacy with increasing age, although the low number of patients in the lowest and highest age groups resulted in wide CIs (Figure 5, *A* and *B*). In the subgroup analyses, there was no consistent effect of age on the efficacy of tiotropium Respimat, neither for patients with severe asthma (Table E1) nor for patients with moderate asthma (Table E2), with more than 50% of patients in all age groups receiving tiotropium Respimat showing clinically relevant improvements from baseline. For salmeterol, there was a trend to decreasing efficacy with increasing age in both the continuum (Figure 5, *B*) and the subgroup (Table E2) analyses.

Safety

The overall frequencies of adverse events and serious adverse events with tiotropium Respimat were unaffected by age, with the percentage of adverse events similar to those observed with placebo (Table II). Asthma serious adverse events (ie, a flare/exacerbation of asthma, based on the preferred term "asthma," Medical Dictionary for Regulatory Activities version 16.1) were reported by 38 patients in PrimoTinA-asthma (17 [3.7%] with tiotropium Respimat 5 μg and 21 [4.6%] with placebo) and 8 patients in MezzoTinA-asthma (2 [0.4%], 1 [0.2%], 2 [0.4%], and 3 [0.6%] with tiotropium Respimat 2.5 and 5 μg, salmeterol, and placebo, respectively).[2,3] There was no consistent relationship between age and occurrence of this event (Table II).

DISCUSSION

Although the studies were not specifically designed to evaluate the effect of age on bronchodilator efficacy or safety in patients with asthma, these *post hoc* analyses were designed to provide useful information about the use of tiotropium in clinical settings. The analyses show that there is no differential age-based response to tiotropium in patients with moderate asthma who were symptomatic on medium-dose ICS alone, or in those with severe asthma not well controlled on combination therapy with high-dose ICS plus LABA.

The lack of an influence of age on tiotropium efficacy was especially evident for the lung function end points. Any differences between age groups were small and not clinically

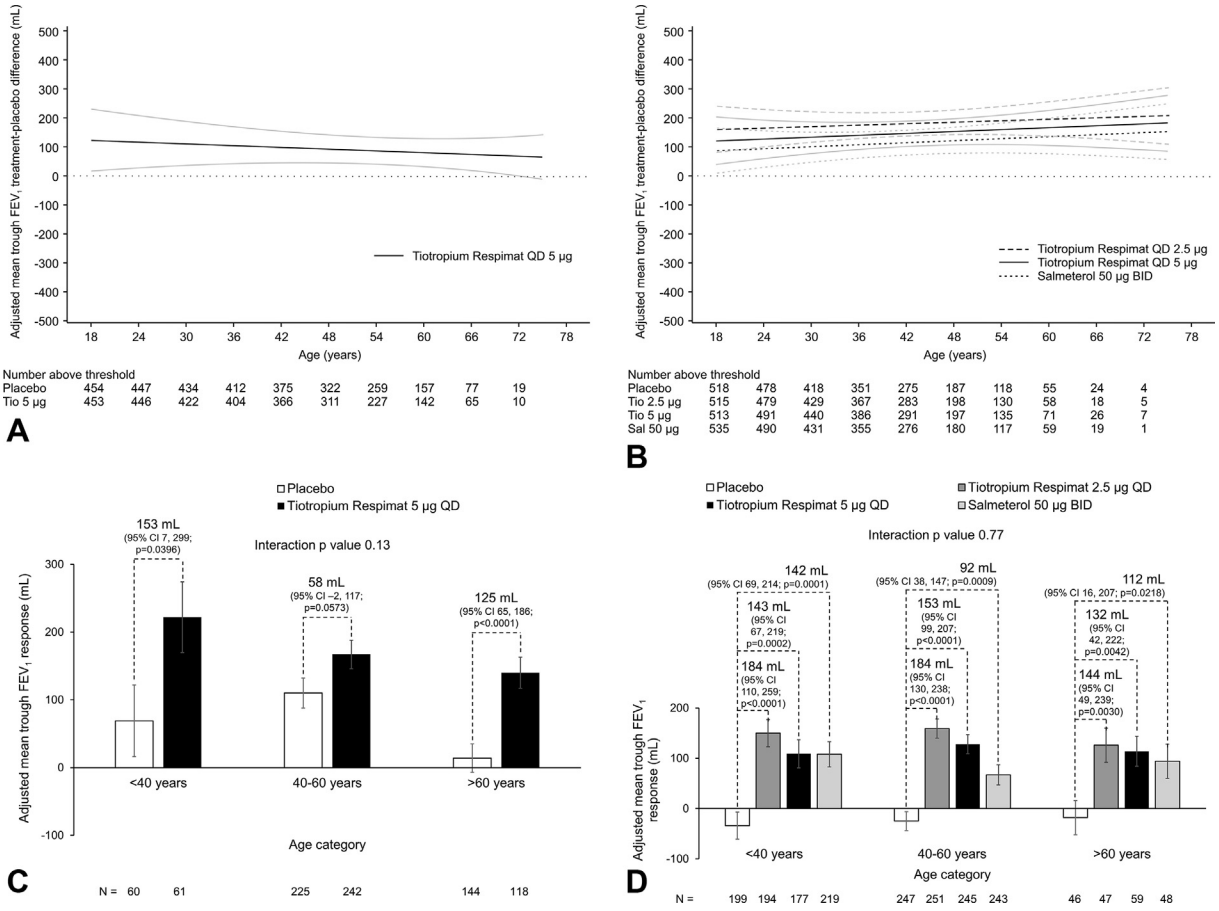

FIGURE 1. Trough FEV_1 at week 24: Adjusted mean treatment-placebo difference continuum analysis in patients with (**A**) severe asthma (PrimoTinA-asthma) and (**B**) moderate asthma (MezzoTinA-asthma), and adjusted mean values and treatment-placebo differences in age categories in patients with (**C**) severe asthma (PrimoTinA-asthma) and (**D**) moderate asthma (MezzoTinA-asthma). *BID*, Twice daily; *QD*, once daily; *Sal*, salmeterol; *Tio*, tiotropium. Full analysis set. Pooled data: (**A** and **C**) add-on to ICS plus LABA; (**B** and **D**) add-on to ICS. Data plotted are adjusted mean treatment-placebo difference and 95% CI in panels **A** and **B**, and adjusted mean ± SE in panels **C** and **D**.

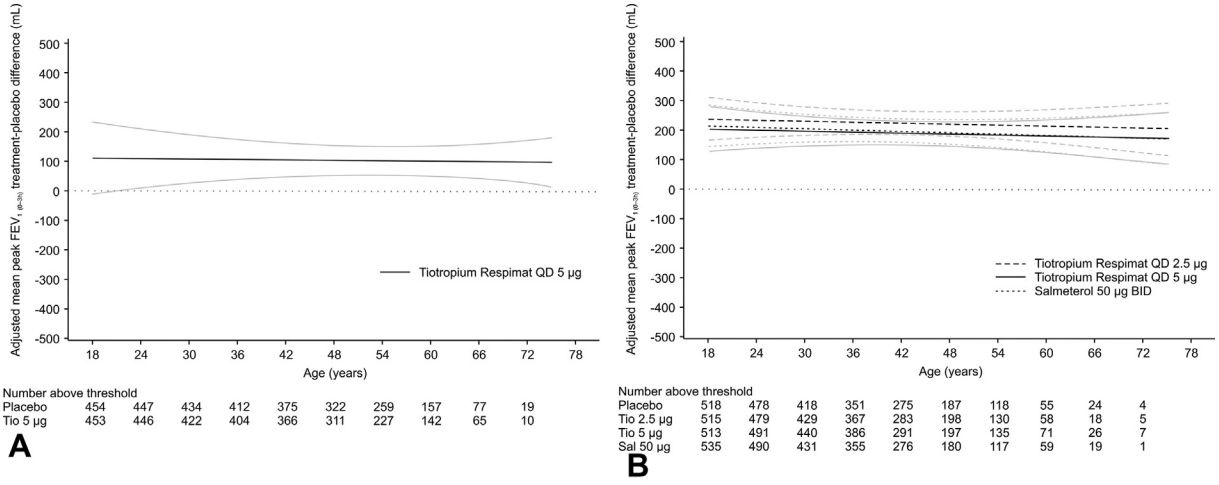

FIGURE 2. Adjusted mean treatment-placebo difference in peak FEV_1 at week 24 in patients with (**A**) severe asthma (PrimoTinA-asthma) and (**B**) moderate asthma (MezzoTinA-asthma). *BID*, Twice daily; *QD*, once daily; *Sal*, salmeterol; *Tio*, tiotropium. Full analysis set. Pooled data: (**A**) add-on to ICS plus LABA; (**B**) add-on to ICS. Data plotted are adjusted mean treatment-placebo difference and 95% CI.

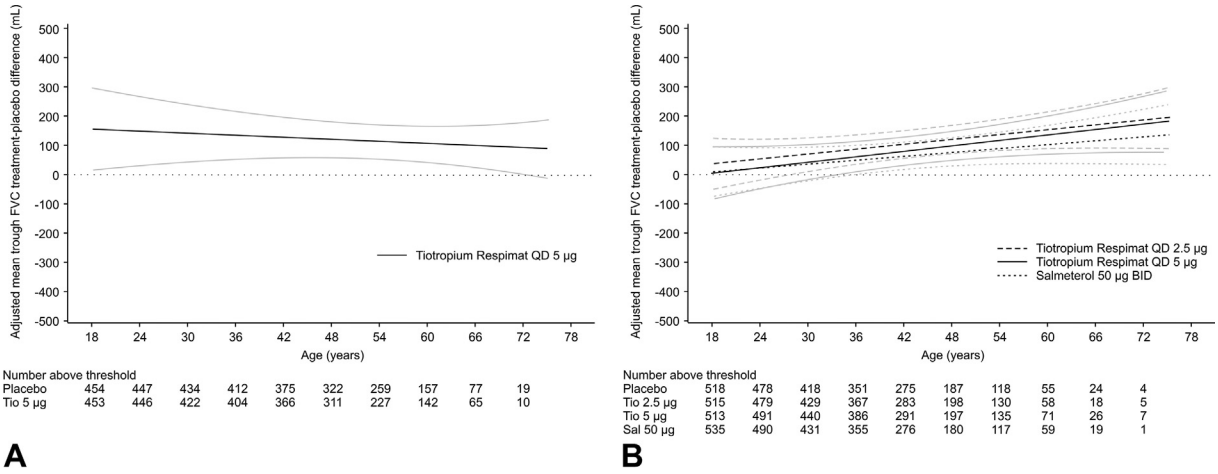

FIGURE 3. Adjusted mean treatment-placebo difference in trough FVC at week 24 in patients with (**A**) severe asthma (PrimoTinA-asthma) and (**B**) moderate asthma (MezzoTinA-asthma). *BID*, Twice daily; *FVC*, forced vital capacity; *QD*, once daily; *Sal*, salmeterol; *Tio*, tiotropium. Full analysis set. Pooled data: (**A**) add-on to ICS plus LABA; (**B**) add-on to ICS. Data plotted are adjusted mean treatment-placebo difference and 95% CI.

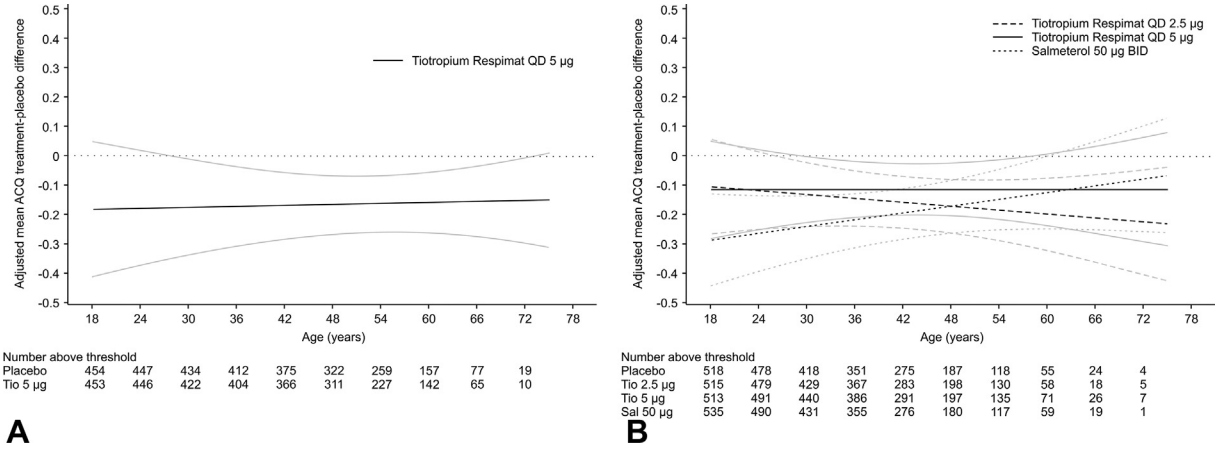

FIGURE 4. Adjusted mean treatment-placebo difference in ACQ total score at week 24 in patients with (**A**) severe asthma (PrimoTinA-asthma) and (**B**) moderate asthma (MezzoTinA-asthma). *BID*, Twice daily; *QD*, once daily; *Sal*, salmeterol; *Tio*, tiotropium. Full analysis set. Pooled data: (**A**) add-on to ICS plus LABA; (**B**) add-on to ICS. Data plotted are adjusted mean treatment-placebo difference and 95% CI.

meaningful neither in patients with moderate nor in patients with severe asthma. Furthermore, the continuum analyses demonstrated no clear or consistent influence of age on lung function. Similarly, for asthma control, age did not influence the overall treatment effect of tiotropium in terms of ACQ total score, neither in the continuum nor in the subgroup analyses. In the responder continuum analyses, there appeared to be a slight fall with increasing age in the odds ratio for response to tiotropium, both in patients with severe asthma and in those with moderate disease. However, the percentages of patients with a clinically relevant improvement in the tiotropium treatment groups was consistently above 50% in all age categories, with no indication of an effect of age. In contrast, the percentage of responders on placebo increased with increasing age in both disease severities, suggesting that the fall in the odds ratio for response observed in the continuum analysis was due to an increasing placebo effect, and not a decrease in tiotropium efficacy.

As with tiotropium, age did not influence the efficacy of salmeterol in terms of the bronchodilator responsiveness end points. With increasing age there was a gradual (although small) fall in the effect of salmeterol on ACQ total score and ACQ responders, in both the continuum and the subgroup analyses. However, the patient numbers were not balanced across age groups (with relatively few patients with moderate asthma older than 60 years), and all interaction *P* values were nonsignificant, indicating that overall there was no impact of age on treatment effect, and so these results should be interpreted with caution. Indeed, in a previous study in adults with asthma (mean age, 42.2 years), tiotropium and salmeterol had similar effects on ACQ mean score, although tiotropium had a significantly greater effect on FEV_1.[9]

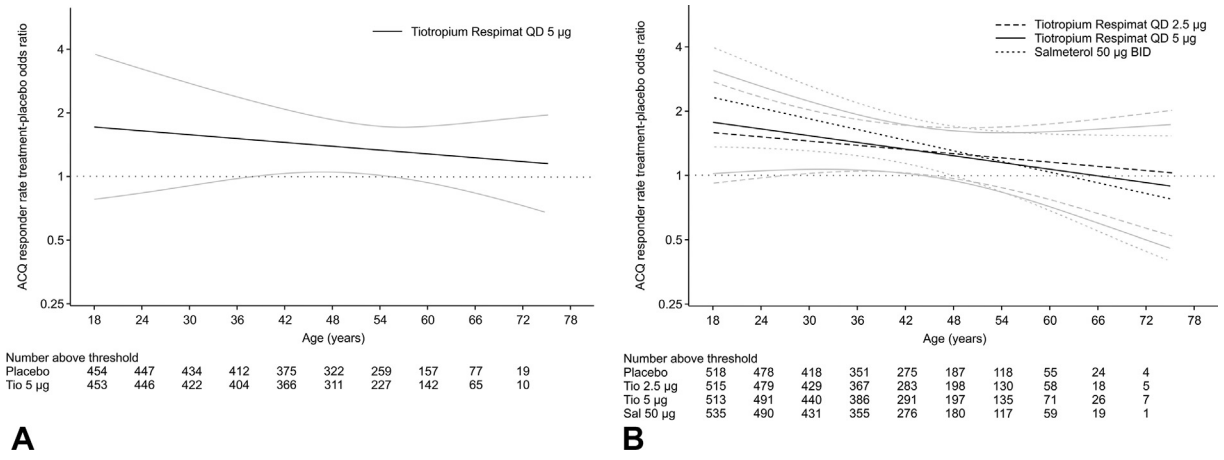

FIGURE 5. Treatment-placebo odds ratio for ACQ response at week 24 in patients with (**A**) severe asthma (PrimoTinA-asthma) and (**B**) moderate asthma (MezzoTinA-asthma). *ACQ*, Asthma Control Questionnaire; *BID*, twice daily; *QD*, once daily; *Sal*, salmeterol; *Tio*, tiotropium. Full analysis set. Pooled data: (**A**) add-on to ICS plus LABA; (**B**) add-on to ICS. Data plotted are treatment-placebo odds ratio and 95% CI.

TABLE II. Overall summary of adverse events

	PrimoTinA-asthma*†		MezzoTinA-asthma*‡			
%	Tiotropium Respimat 5 µg QD (n = 456)	Placebo (n = 456)	Tiotropium Respimat 2.5 µg QD (n = 519)	Tiotropium Respimat 5 µg QD (n = 517)	Salmeterol 50 µg BID (n = 541)	Placebo (n = 523)
Any adverse event						
<40 y	73.9	79.1	61.2	58.5	55.3	53.9
40-60 y	73.6	79.9	57.1	59.0	52.2	62.0
>60 y	72.9	81.3	51.0	46.0	60.8	66.7
Asthma§ adverse events						
<40 y	44.9	50.7	15.8	23.3	20.3	20.7
40-60 y	40.7	53.1	17.8	19.5	17.0	23.6
>60 y	35.7	47.3	5.9	23.8	27.5	18.8
Serious adverse events						
<40 y	10.1	6.0	2.4	1.6	1.3	1.8
40-60 y	7.4	8.8	1.9	2.3	1.6	2.7
>60 y	8.5	10.0	3.9	3.2	7.8	6.3
Asthma§ serious adverse event						
<40 y	8.7	4.5	0.5	0	0	0.5
40-60 y	3.1	5.0	0.4	0	0.8	0.8
>60 y	2.3	4.0	0	1.6	0	0

BID, Twice daily; *QD*, once daily.
Treated set.
*Pooled data, with percentages calculated using the number of patients in the treatment group and age category as denominator.
†Add-on to ICS plus LABA.
‡Add-on to ICS.
§Based on the preferred term "asthma," Medical Dictionary for Regulatory Activities version 16.1.

There is a perception that β_2-agonists are more effective in younger patients, whereas muscarinic antagonists may be more effective in older patients. Some early preclinical studies suggested that age had an impact on the activity or function of β_2 or muscarinic receptors,[10-14] although this was not found in other preclinical studies.[15,16] The perception of differential efficacy is perhaps based on a clinical trial conducted nearly 30 years ago in patients with mild or moderate airflow limitation, in which those younger than 60 years tended to have a greater response to albuterol, whereas individuals older than 60 years tended to have a greater response to ipratropium.[5] However, the study recruited both patients with asthma and those with chronic obstructive pulmonary disease from general medical practice settings. In the subgroup of patients with asthma, although there was a slight trend to decreasing efficacy with age for albuterol, age had no significant influence on the efficacy of ipratropium.[5] Similarly, in a study that only evaluated patients with asthma, although the efficacy of both albuterol and ipratropium was lower in older than younger patients, within each age group responses to albuterol and ipratropium were similar.[17] Likewise, in a study that recruited patients with stable asthma, both albuterol and ipratropium were effective in younger (18-25 years) and older

(>65 years) patients, and age was not a predictor of response to either drug.[18] These studies demonstrate the importance of recruiting appropriate patient populations; all of the MezzoTinA-asthma studies (which used medium-dose ICS) and PrimoTinA-asthma studies (which used high-dose ICS plus long-acting bronchodilators) specifically recruited patients with asthma, excluding those with chronic obstructive pulmonary disease, and showed results that were consistent with previous asthma studies that used short-acting bronchodilators. The MezzoTinA-asthma data extend and expand these previous data using 2 long-acting bronchodilators: tiotropium showed similar effectiveness across the age groups studied in terms of both lung function and asthma control, with the effectiveness of salmeterol on lung function not impacted by age. Importantly, all treatments were well tolerated, with adverse event profiles similar to placebo without evidence that side effects varied with age.

The main limitation of the analyses in this study is the variation in sizes of the patient subgroups, and especially the relatively small sizes of the younger than 40 years category in the 2 PrimoTinA-asthma studies and the older than 60 years category in the 2 MezzoTinA-asthma studies. However, the consistency of the tiotropium data across all end points in the 2 pairs of studies suggest that our findings are unlikely to be substantially impacted by the sizes of these subgroups. In addition, these analyses were not formally powered, and lack of statistical significance of a treatment-by-age subgroup interaction from such analyses should be interpreted with caution. A prospective, suitably designed study would be required to confirm the findings. Of course, care should be taken when extrapolating the data from any randomized controlled trial (where inclusion and exclusion criteria were applied to select patients) to real life.

CONCLUSIONS

Once-daily tiotropium add-on to ICS or ICS/LABA therapy improved lung function and was effective and well tolerated in patients with symptomatic asthma independent of age. The analyses clearly show that the bronchodilator effects of antimuscarinic therapy with tiotropium are similar in younger and older patients, and so provide evidence that differs from the perception that there is a reduced bronchodilator response in the elderly. These findings have important therapeutic implications, because there is an increase in the aging population worldwide as well as increased prevalence of asthma in older individuals.

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TABLE E1. ACQ total score and responders at week 24 in patients with severe asthma (PrimoTinA-asthma)

Age group	Tiotropium Respimat 5 μg QD	Placebo
<40 y		
Adjusted mean ± SE	1.934 ± 0.093 (N = 61)	2.214 ± 0.094 (N = 60)
Active-placebo difference, adjusted mean (95% CI; *P* value)*	−0.280 (−0.540 to −0.021; .0341)	
Patients with a clinically relevant improvement,† n/N (%)	36/69 (52.2)	26/67 (38.8)
40-60 y		
Adjusted mean ± SE	2.038 ± 0.046 (N = 241)	2.156 ± 0.048 (N = 224)
Active-placebo difference, adjusted mean (95% CI; *P* value)*	−0.118 (−0.250 to 0.013; .0766)	
Patients with a clinically relevant improvement,† n/N (%)	137/256 (53.5)	114/238 (47.9)
>60 y		
Adjusted mean ± SE	1.991 ± 0.059 (N = 121)	2.153 ± 0.055 (N = 141)
Active-placebo difference, adjusted mean (95% CI; *P* value)*	−0.163 (−0.321 to −0.004; .0444)	
Patients with a clinically relevant improvement,† n/N (%)	71/128 (55.5)	73/149 (49.0)

QD, Once daily; *SE*, standard error.
Full analysis set. Pooled data: add-on to ICS plus LABA. N is the number of patients with measurements at the respective time point.
*Interaction *P* value .13.
†Defined as an improvement in ACQ score of at least 0.5 points from baseline.

TABLE E2. ACQ total score and responders at *w*eek 24 in patients with moderate asthma (MezzoTinA-asthma)

Age group	Tiotropium Respimat 2.5 μg QD	Tiotropium Respimat 5 μg QD	Salmeterol 50 μg BID	Placebo
<40 y				
Adjusted mean ± SE	1.314 ± 0.048 (N = 193)	1.347 ± 0.050 (N = 178)	1.197 ± 0.045 (N = 219)	1.483 ± 0.047 (N = 196)
Active-placebo difference, adjusted mean (95% CI; *P* value)*	−0.169 (−0.301 to −0.037; .0121)	−0.136 (−0.271 to −0.001; .0482)	−0.286 (−0.414 to −0.158; <.0001)	
Patients with a clinically relevant improvement,† n/N (%)	132/208 (63.5)	127/192 (66.1)	162/234 (69.2)	120/216 (55.6)
40-60 y				
Adjusted mean ± SE	1.367 ± 0.043 (N = 252)	1.439 ± 0.044 (N = 245)	1.407 ± 0.044 (N = 242)	1.534 ± 0.044 (N = 246)
Active-placebo difference, adjusted mean (95% CI; *P* value)*	−0.167 (−0.287 to −0.046; .0067)	−0.095 (−0.216 to 0.026; .1219)	−0.127 (−0.248 to −0.006; .0405)	
Patients with a clinically relevant improvement,† n/N (%)	168/257 (65.4)	160/258 (62.0)	162/250 (64.8)	150/254 (59.1)
>60 y				
Adjusted mean ± SE	1.473 ± 0.098 (N = 47)	1.463 ± 0.088 (N = 59)	1.458 ± 0.098 (N = 48)	1.568 ± 0.101 (N = 45)
Active-placebo difference, adjusted mean (95% CI; *P* value)*	−0.095 (−0.372 to 0.182; .4997)	−0.106 (−0.369 to 0.158; .4308)	−0.110 (−0.387 to 0.167; .4362)	
Patients with a clinically relevant improvement,† n/N (%)	32/50 (64.0)	43/63 (68.3)	32/51 (62.7)	29/48 (60.4)

BID, Twice daily; *QD*, once daily.

Full analysis set. Pooled data: add-on to ICS. N is the number of patients with measurements at the respective time point.

*Interaction *P* value .49.

†Defined as an improvement in ACQ score of at least 0.5 points from baseline.

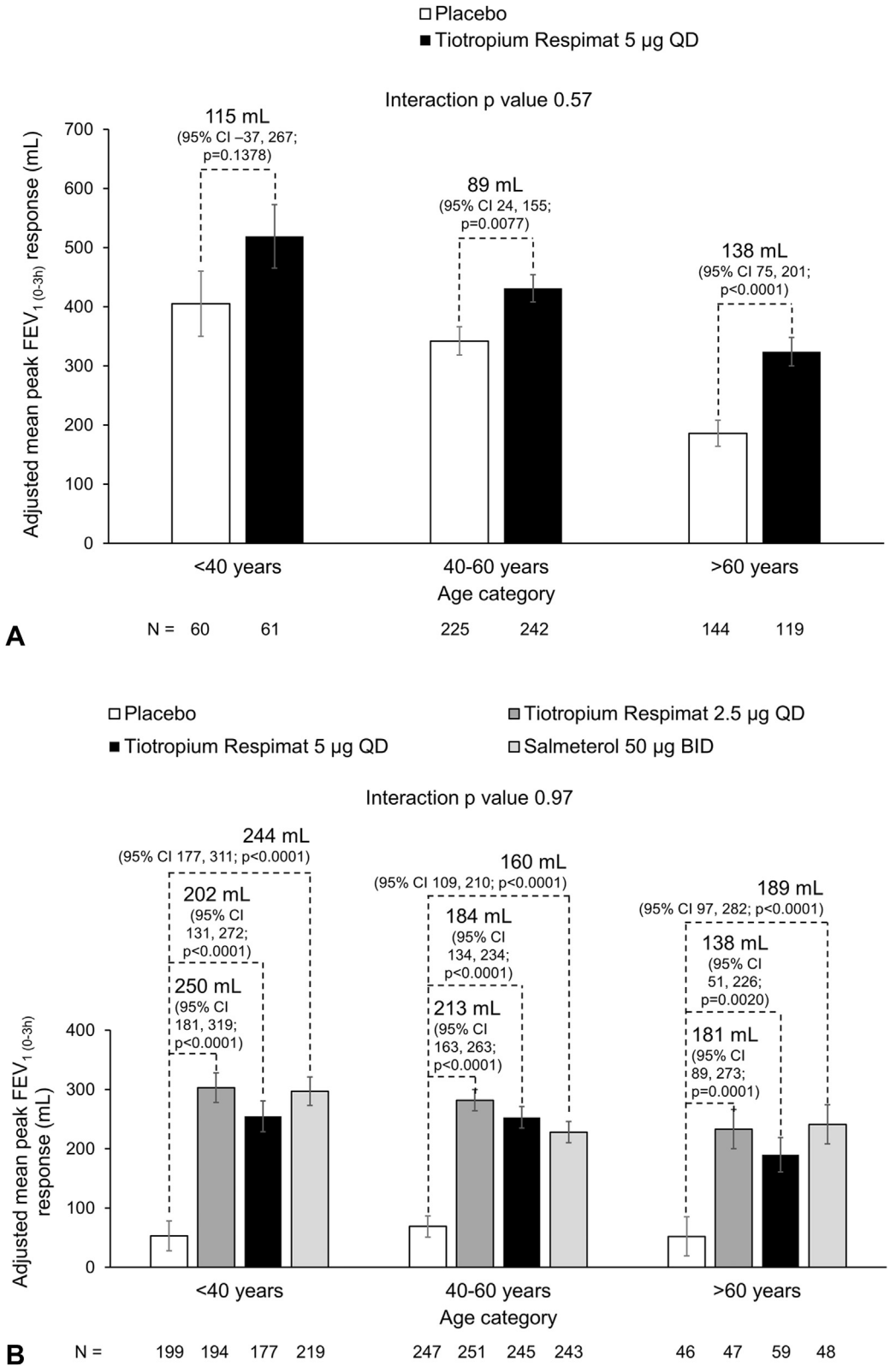

FIGURE E1. Adjusted mean peak FEV_1 and treatment-placebo differences at week 24 in patients with (**A**) severe asthma (PrimoTinA-asthma) and (**B**) moderate asthma (MezzoTinA-asthma). *BID*, Twice daily; *QD*, once daily. Full analysis set. Pooled data: (**A**) add-on to ICS plus LABA; (**B**) add-on to ICS. Data plotted are adjusted mean ± SE.

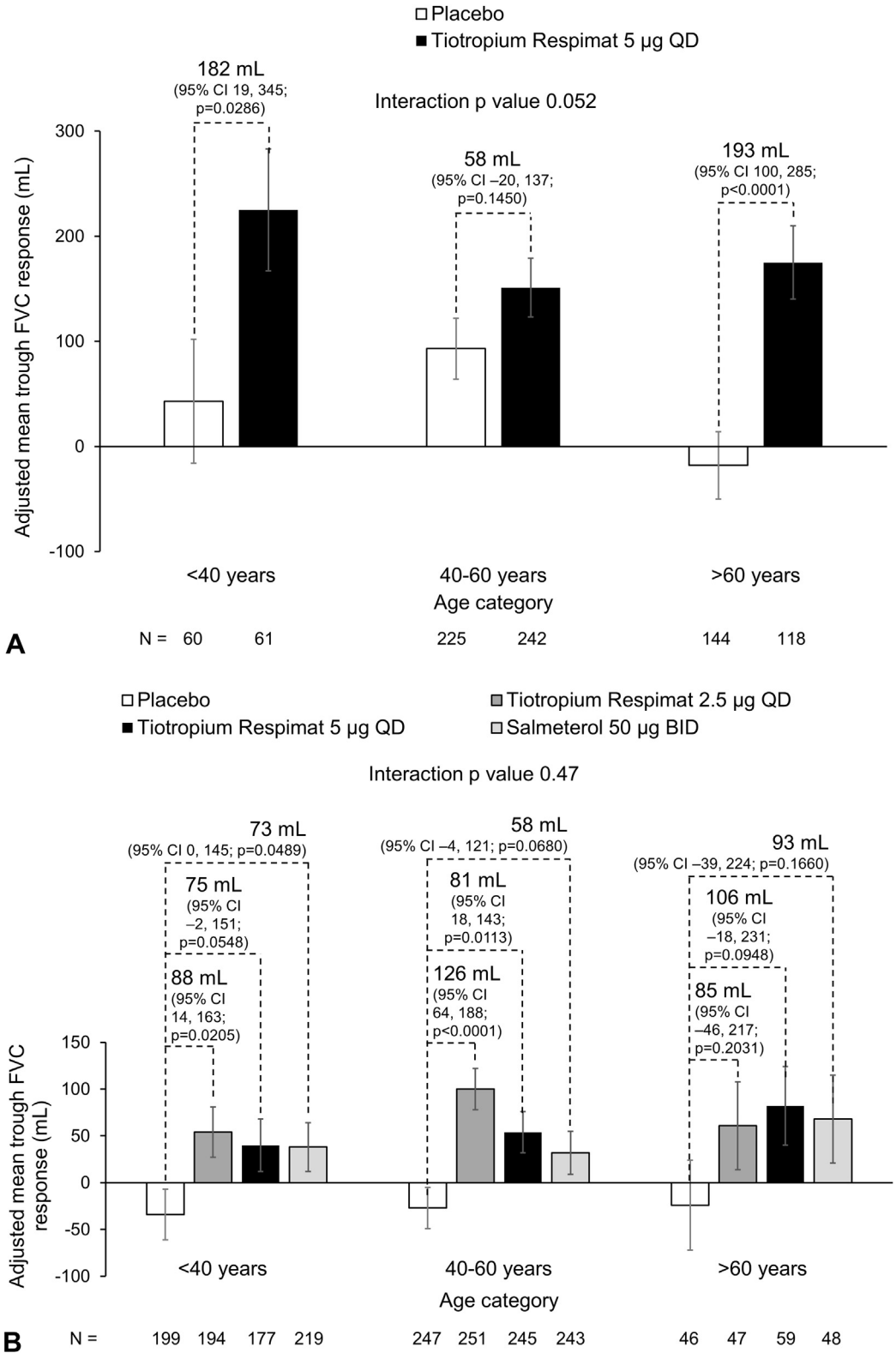

FIGURE E2. Adjusted mean trough FVC and treatment-placebo differences at week 24 in patients with (**A**) severe asthma (PrimoTinA-asthma) and (**B**) moderate asthma (MezzoTinA-asthma). *BID*, Twice daily; *FVC*, forced vital capacity; *QD*, once daily. Full analysis set. Pooled data: (**A**) add-on to ICS plus LABA; (**B**) add-on to ICS. Data plotted are adjusted mean ± SE.